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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/536,860	01/06/2006	Hana Golding	65831 (47992)	4611

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EXAMINER	
CHEN, STACY BROWN	
ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/536,860	GOLDING, HANA	
	Examiner	Art Unit	
	Stacy B. Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,7,12-15,17,18,21 and 130-136* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,7,12-15,17,18,21 and 130-136* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 May 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 10, 2010 has been entered. Claims 1, 5, 7, 12-15, 17, 18, 21 and new claims 130-136 are pending and under examination.

Response to Arguments

2. Upon further consideration of the teachings of the prior art references of record, the rejection of claims 1, 3-5, 7, 12-15 and 17 under 35 U.S.C. 103(a) as being unpatentable over Domínguez *et al.* (*Journal of Immunological Methods*, 1998, 220:115-221, "Domínguez") in view of Hooper *et al.* (US Patent 6,451,309, "Hooper") is withdrawn, as is the rejection of claims 18 and 21 under 35 U.S.C. 103(a) as being unpatentable over Domínguez *et al.* (*Journal of Immunological Methods*, 1998, 220:115-221, "Domínguez") in view of Hooper *et al.* (US Patent 6,451,309, "Hooper") as applied to claims 1 and 17 above, and further in view of Engelmayer *et al.* (*The Journal of Immunology*, 1999, 163:6762-6768, "Engelmayer"). Applicant's arguments were fully considered and found persuasive in part with respect to the argument that the motivation to use the GFP-vaccinia infection tag of Domínguez in Hooper's method is not reasonably explained by Hooper's remarks concerning the lack of *in vivo* predictability as a result of *in vitro* neutralization tests. By incorporating the infection tag of Domínguez into Hooper's

method, the resulting method still remains an *in vitro* method that does not provide any more information regarding predictability *in vivo*. New grounds of rejection are set forth below.

Claims Summary

3. The claims are drawn to a method comprising:

- Incubating a mixture of at least one cell, a candidate agent, and a labeled virus (invasin) that encodes a detectable label under conditions wherein the virus can invade the cell
- Detecting the detectable label within the cell, wherein a decrease of the label in the cell indicates that the candidate agent decreases virus invasion of the cell.

Specifically, the virus is an enveloped virus, such as vaccinia. The detectable label is a fluorescent protein or an enzyme. The candidate agent is a monoclonal, a polyclonal or altered antibody. An altered antibody includes antibody fragments described on page 11, lines 13-16. The candidate agent associates with the labeled invasin. The Office interprets "associates with" to be equivalent to the antibody binding the invasin. Specifically, the cell is a mammalian cell, such as a human cell (*e.g.*, lymphoid, pulmonary or intestinal).

The method is in the format of a neutralization assay or a high throughput assay and may be performed in a 96-well plate. The method may also include quantitation of invasion of a cell by a virus using a standard curve, wherein r^2 of the standard curve is >0.9. The method results correlate with viral lethality *in vivo* and are comparable to results obtained with the classic PRNT neutralization assays.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 130, 132 and 136 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 130 and 132 recite the limitation "the assay" in referencing claim 1. There is insufficient antecedent basis for this limitation in the claim. If Applicant means that the format of the method is a neutralization assay or a high throughput assay, then the claims should be amended to reflect this concept. The term "comprising" implies that there are extra steps to be performed for the neutralization assay or high throughput assay after the initial steps of the claim 1 are accomplished.

Claim 136 recites, "wherein the method provides results are comparable to results obtained with the classic PRNT neutralization assays". The term "classic" is relative and subject to individual interpretation. The metes and bounds of the claim cannot be clearly determined without a definitive understanding of what is encompassed by "classic" with respect to PRNT neutralization assays.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 5, 7, 12-15, 17, 18, 21, 130, 131 and 136 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hooper *et al.* (US Patent 6,451,309, "Hooper") in view of Auewarakul *et al.* (*Asian Pacific Journal of Allergy and Immunology*, 2001, 19:139-144, cited in IDS filed 3/29/07, "Auewarakul") and Domínguez *et al.* (*Journal of Immunological Methods*, 1998, 220:115-221, "Domínguez").

Hooper teaches the production and identification of vaccinia monoclonal antibodies for the purpose of therapeutic treatment (passive immunization) of vaccinia in humans (abstract). Hooper discloses that potential targets for poxvirus therapeutics, monoclonal antibodies, were generated in mice and tested for their ability to neutralize virus and protect mice from challenge (col. 2, lines 5-20).

It would have been obvious to have modified Hooper's method by using methods known in the art to improve the speed of the assay and also decrease the cost of performing plaque reduction neutralization testing. One would have been motivated to use a reporter virus in a neutralizing antibody assay using flow cytometry as a measurement tool, such as the assay described by Auewarakul in order to test the many antibodies of Hooper with greater speed and reduced cost (see abstract). Although Auewarakul's reporter virus is an HIV construct, it would have been obvious to have used Domínguez' green fluorescent protein (GFP) recombinant vaccinia virus that permits early detection of infected cells by flow cytometry (abstract). Domínguez uses the construct as an infection tag (page 116, first column, third full paragraph). One would have expected Domínguez' reporter virus to infect Hooper's cells (if not neutralized by antibodies) and express GFP, which would then be detected by flow cytometry.

With regard to the limitation of claim 13 which requires that the detectable label be an enzyme, Domínguez discloses that a number of marker genes have been inserted in the vaccinia virus genome, and that their utility has been demonstrated in different experimental situations (thymidine kinase, guanine phosphoribosyl transferase, beta-galactosidase, etc.), see Domínguez, pages 115-116, bridging paragraph. Although Domínguez opts to use GFP, it is clear that enzyme labels are well known in the art to be useful in vaccinia infectivity assays. It would have been well within the ability of the ordinary artisan to elect whether to use GFP or an enzyme label depending on the circumstances of the assay.

With regard to the limitations of claims 18 and 21, that the cells be human (e.g., lymphoid), it would have been obvious to have used human cells in the method in order to reflect more accurately the infection of human cells by vaccinia. Auewarakul uses human PBMCs in their HIV-1 neutralization assay (see pages 140-141, bridging col.).

With regard to the limitation in claim 131 that the method results correlate with viral lethality *in vivo*, one would expect some degree of correlation between *in vitro* results and *in vivo* results. For example, it is usually through *in vitro* testing that candidate *in vivo* products are selected and tested further for efficacy. With regard to the limitation in claim 136 that the method provides results that are comparable to results obtained with the classic PRNT neutralization assays, the results are expected to be comparable, given that Auewarakul's reporter-virus flow cytometry method yielded comparable results to the standard infectivity reduction assay (see Auewarakul, abstract). Therefore, the invention would have been obvious to one of ordinary skill in the art at the time of the invention.

6. Claims 132 and 135 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hooper *et al.* (US Patent 6,451,309, "Hooper") in view of Auewarakul *et al.* (*Asian Pacific Journal of Allergy and Immunology*, 2001, 19:139-144, cited in IDS filed 3/29/07, "Auewarakul") and Domínguez *et al.* (*Journal of Immunological Methods*, 1998, 220:115-221, "Domínguez"), as applied to claim 1 above, and further in view of Briskin *et al.* (US Patent 6,319,675, published November 20, 2001, filed November 24, 1999, "Briskin") and BD Biosciences (*Introduction to Flow Cytometry: A Learning Guide*, Manual Part Number: 11-11032-01, April, 2000, "the flow cytometry guide"). The claims require that the assay be a high throughput assay. The method is performed in a 96-well plate. These particular limitations are not taught by Hooper, Auewarakul or Domínguez.

However, it would have been obvious to have applied high throughput technology to the method taught by Hooper/Auewarakul/Domínguez in order to process more samples (e.g., antibodies) in less time. Briskin's teachings are an example of the technology available at the time of the invention with regard to high throughput screening. Although Briskin's assays are directed to different products, the concept of screening large numbers of samples (in 96-well plates, for example) for potential agents that interfere with various binding partners was known (see col. 16, lines 42-54). Therefore, the invention would have been obvious to one of ordinary skill in the art at the time of the invention.

7. Claims 133 and 134 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hooper *et al.* (US Patent 6,451,309, "Hooper") in view of Auewarakul *et al.* (*Asian Pacific Journal of Allergy and Immunology*, 2001, 19:139-144, cited in IDS filed 3/29/07,

"Auewarakul") and Domínguez *et al*. (*Journal of Immunological Methods*, 1998, 220:115-221, "Domínguez"), as applied to claim 1 above, and further in view of BD Biosciences (*Introduction to Flow Cytometry: A Learning Guide*, Manual Part Number: 11-11032-01, April, 2000, "the flow cytometry guide"). The claimed method further comprises quantitation of invasion of a cell using a standard curve, wherein r^2 of the standard curve is >0.9. These particular limitations are not taught by Hooper, Auewarakul or Domínguez.

However, it would have been obvious to have quantified the results of the method in order to have more accurate measurements of the various antibodies' neutralization capabilities. One would have followed the guidelines available to those of ordinary skill in the art, such as the flow cytometry guide. In order to quantitate the results, one would have to have a standard curve (see the flow cytometry guide, page 35). As for the r^2 being >0.9, the ordinary artisan would have selected any optimal value subject to individual preference. Therefore, the invention would have been obvious to one of ordinary skill in the art at the time of the invention.

Conclusion

8. No claim is allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would

like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30), alternate Fridays off,. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Zachariah Lucas can be reached on 571-272-0905. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Stacy B Chen/
Primary Examiner, Art Unit 1648